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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/473,830	12/28/1999	JEFFREY M. LEIDEN	2844/53802	1518

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HALE AND DORR LLP
300 PARK AVENUE
NEW YORK, NY 10022

EXAMINER
CHEN, SHIN LIN

ART UNIT	PAPER NUMBER
1632	

DATE MAILED: 09/10/2003

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	09/473,830	LEIDEN ET AL.	
	Examiner	Art Unit	
	Shin-Lin Chen	1632	

-- The MAILING DATE f this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *24 June 2003* .

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *24-30,32,33 and 35-46* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *24-30,32,33 and 35-46* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

11)☐ The proposed drawing correction filed on _____ is: a)☐ approved b)☐ disapproved by the Examiner.

If approved, corrected drawings are required in reply to this Office action.

12)☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. §§ 119 and 120

13)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____ .

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

14)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. § 119(e) (to a provisional application).

a) ☐ The translation of the foreign language provisional application has been received.

15)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449) Paper No(s) _____ .
4) ☐ Interview Summary (PTO-413) Paper No(s). _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other:

DETAILED ACTION

Applicants' appeal brief filed 6-24-03 has been entered. Upon further consideration of the claimed invention, the finality of the Official action mailed 9-24-02 (Paper No. 22) has been withdrawn.

Claim Rejections - 35 USC § 112

1. The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

2. Claim 42 is rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

The phrase "said desired molecule is an ion channel gene...a protein or nucleic acid capable of inducing angiogenesis" in claim 42 is vague and renders the claim indefinite. Claim 24 reads on a nucleic acid encoding a desired molecule. It was known in the art that expression of a nucleic acid produces a RNA or eventually a protein from the translation of the RNA. It is unclear how a nucleic acid encodes **a gene or nucleic acid capable of inducing angiogenesis**.

The phrase "a contractile protein" in claim 42 is vague and renders the claim indefinite. It is unclear as to the metes and bounds of what would be considered "a contractile protein". The specification fails to specifically define the phrase "a contractile protein".

Claim Rejections - 35 USC § 112

3. The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it

pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

4. Claims 41, 42, 44 and 46 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for a method of introducing an AAV vector expressing an angiogenic protein, such as FGF protein and VEGF protein, into cardiomyocytes via intracoronary injection so as to ameliorate the symptom of a hear disease as disclosed by Hammond et al., 1998 (WO 98/50079), does not reasonably provide enablement for a method of introducing an AAV vector expressing any protein or antisense RNA other than angiogenic protein into cardiomyocytes via intracoronary injection so as to provide therapeutic effect in vivo for a particular disease, such as hear disease. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to use the invention commensurate in scope with these claims.

Claims 41, 42, 44 and 46 are directed a method of introducing an AAV vector expressing a desired molecule, such as an antisense RNA, an ion channel gene, a contractile protein, a beta-adrenergic receptor or kinase, a phospholamban, a thymidine kinase, p21, and p27 etc., into cardiomyocytes by infusing said AAV vector into a coronary artery or a coronary sinus of an animal in an amount of $1x10^5$ to $1x10^9$ IU/gm body weight. Claim 46 specifies the desired molecule has an effect in inducing angiogenesis, inhibiting angiogenesis, stimulating or inhibiting cell proliferation, treating restenosis, treating atherosclerosis, treating congestive heart disease, treating ischemic cardiomyopathy, or treating malignant arrhythmia.

The specification discloses transducing explanted and perfused hearts of C57BL/6 mice with 1.5x19E9 IU of AAV/CMV-lacZ for 15 minutes via catheter in the left common carotid artery, and the hearts were transplanted into the necks of syngeneic hosts and the arterial

circulation reestablished by anastomosis of the transplanted aorta to the recipient carotid artery, The results suggest that 4 weeks after perfusion about 40% of cardiomyocytes were beta-galactosidase positive, a number which increased to greater that 50% several weeks post transplantation.

The specification states "The ability to stably and efficiently program recombinant gene expression in cardiomyocytes facilitates gene therapy approaches for a variety of cardiovascular disease and conditions" and "The present invention is directed to a method of treating a cardiovascular condition by infusing an rAAV vector into a coronary artery or a coronary sinus for a time and in an amount sufficient to stably efficient transduce the cardiomyocytes perfused to the artery or sinus" (see specification, page 1, 3). The claims read on gene therapy *in vivo* for a variety of cardiovascular diseases and conditions in light of the specification as discussed above.

The claims encompass introducing an AAV vector expressing a desired molecule, such as an antisense RNA, an ion channel gene, a contractile protein, a beta-adrenergic receptor or kinase, a phospholamban, a thymidine kinase, p21, and p27 etc., into cardiomyocytes by infusing said AAV vector into a coronary artery or a coronary sinus of an animal in an amount of $1x10^5$ to $1x10^9$ IU/gm body weight so as to induce angiogenesis, inhibit angiogenesis, stimulate or inhibit cell proliferation, treat restenosis, treat atherosclerosis, treat congestive heart disease, treat ischemic cardiomyopathy, or treat malignant arrhythmia.

The specification fails to provide adequate guidance and evidence for the correlation of a desired molecule encoded by the nucleic acid set forth above with a particular cardiovascular disease or condition. The specification also fails to provide adequate guidance and evidence

whether the desired molecule would be expressed and be present in a sufficient amount at the targeted site such that said desired molecule could provide therapeutic effect for a particular cardiovascular disease or condition in a patient *in vivo*.

The sufficient amount of desired molecules encoded by different genes for providing therapeutic effect in a patient *in vivo* for a particular cardiovascular disease or condition could vary dramatically because of different functions of the desired molecules and the targeted cardiovascular disease or condition. The state of the prior art of gene therapy *in vivo* was not well developed and was highly unpredictable at the time of the invention. Verma et al., 1997 (Nature, Vol. 389, p. 239-242) states that out of the more than 200 clinical trials currently underway, no single outcome can be pointed to as a success story (see Verma et al., page 239, col. 1). For instance, numerous factors complicate the gene therapy art which have not been shown to be overcome by routine experimentation. Eck et al., 1996 (Goodman & Gilman's The Pharmacological Basis of Therapeutics, McGraw-Hill, New York, p. 77-101) indicates that the fate of the DNA vector itself (volume of distribution, rate of clearance into the tissues, etc.), the *in vivo* consequences of altered gene expression and protein function, the fraction of vector taken up by the target cell population, the trafficking of the genetic material within cellular organelles, the rate of degradation of the DNA, the level of mRNA produced, the stability of the mRNA produced, the amount and stability of the protein produced, and the protein's compartmentalization within the cell, or its secretory fate, once produced are all important factors for a successful gene therapy *in vivo*. These factors differ dramatically based on the vector used, the protein being produced, and the disease being treated (e.g. bridging pages 81-

82). Verma et al. states that one major obstacle to success has been the inability to deliver genes efficiently and obtain sustained expression (see Verma et al., page 239, col. 3).

Gene therapy protocols using nucleotide sequences encoding different proteins differ from each other because different proteins have different biological functions and their stabilities inside cells and corresponding disease to be treated could vary. Different diseases differ from each other pathologically and they require nucleic acids encoding different proteins for treatment. The mechanisms of antisense RNA and nucleic acid encoding a therapeutic protein for treating a heart disease differ from each other and require separate consideration in the context of gene therapy in vivo. Therefore, gene therapy using nucleotide sequences encoding different proteins or antisense RNA for various diseases are considered case by case. A successful gene therapy protocol can not be extrapolated into a successful result for another gene therapy protocol. In the present invention, the claims encompass using nucleic acids encoding various proteins, such as ion channel protein, beta-adrenergic receptor or kinase, a phospholamban, a thymidine kinase, p21, and p27 etc. or antisense RNAs to treat various heart diseases, however, there is no evidence of record that a AAV vector expressing a protein other than angiogenic protein can provide therapeutic effect for a heart disease in vivo via intracoronary injection of said AAV vector. The specification fails to provide adequate guidance for how expression of an ion channel protein, a contractile protein, a phospholamban, a beta adrenergic kinase or receptor, p21, p27, p53, rb or NF-kapaB in myocardiocytes would provide therapeutic effect for treating various cardiovascular disease in vivo.

Thus, one skilled in the art at the time of the invention would not know how to use the claimed invention and would require undue experimentation to practice over the full scope of the

invention claimed. This is particularly true given the nature of the claimed invention, the state of the art, the unpredictability found in the art, the teaching and working examples provided, and the breadth of the claims.

Applicants cite Dr. Phamacek's declaration and argue that construction of AAV vector is routine, many proteins and antisense RNA sequences are useful for treating cardiovascular disease, in vivo intracardiac injection of AAV vector provide prolonged expression of beta-galactosidase, intraventricular injection of AAV encoding AT1-R antisense RNA reduced blood pressure and slowed the development of hypertension in rats, and Factor IX, AADC and CFTR are shown to be expressed in various organs of animals by using AAV vector (appear brief, p. 6-8, 27-29). This is not found persuasive because of the reasons set forth above under 35 U.S>C. 112 first paragraph rejection. The unpredictability of the art of gene therapy in vivo is as discussed above. Gene therapy protocols using nucleotide sequences encoding different proteins differ from each other because different proteins have different biological functions and their stabilities inside cells and corresponding disease to be treated could vary. Different diseases differ from each other pathologically and they require nucleic acids encoding different proteins for treatment. The mechanisms of antisense RNA and nucleic acid encoding a therapeutic protein for treating a heart disease differ from each other and require separate consideration in the context of gene therapy in vivo. Therefore, gene therapy using nucleotide sequences encoding different proteins or antisense RNA for various diseases are considered case by case. A successful gene therapy protocol can not be extrapolated into a successful result for another gene therapy protocol. The state of the art in gene therapy in vivo and the teaching of the present

invention fail to provide sufficient enabling disclosure to enable the full scope of the invention claimed.

Claim Rejections - 35 USC § 102

5. The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless –
>
> (a) the invention was known or used by others in this country, or patented or described in a printed publication in this or a foreign country, before the invention thereof by the applicant for a patent.

6. Claims 24, 32, 33, 40, 43 and 45 are rejected under 35 U.S.C. 102(a) as being anticipated by Hammond et al., 1998 (WO 98/50079).

Claims 24, 32, 33, 40, 43 and 45 directed a method of introducing an AAV vector expressing a desired molecule, such as FGF and VEGF, into cardiomyocytes by infusing said AAV vector into a coronary artery or a coronary sinus of an animal in an amount of $1x10^5$ to $1x10^9$ IU/gm, $1x10^7$ IU/gm, or $1x10^6$ to $1x10^8$ IU/gm body weight.

Hammond teaches a method for treating patient with congestive heart failure by delivering an AAV vector expressing FGF or VEGF to said patient via direct intracoronary injection of said AAV vector into coronary artery in an amount of AAV virus of 10^6-10^{14} particles or 10^8-10^{12} particles (e.g. p. 68-71). If a patient's average body weight is 60 kg, i.e. 60000gm, the amount of AAV virus injected to each patient would be 17 to $1.7x10^9$ particles/gm or $1.7x10^3$ to $1.7x10^7$ particles/gm body weight. The range of the AAV virus administered in the present invention falls within the range of the AAV virus taught by Hammond. Thus, claims 24, 32, 33, 40, 43 and 45 are anticipated by Hammond.

Claim Rejections - 35 USC § 103

7. The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

8. This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(e), (f) or (g) prior art under 35 U.S.C. 103(a).

9. Claims 24-30 and 35-39 are rejected under 35 U.S.C. 103(a) as being unpatentable over Hammond et al., 1998 (WO 98/50079).

Claims 24-30 and 35-39 are directed a method of introducing an AAV vector expressing a desired molecule, such as FGF and VEGF, into cardiomyocytes by infusing said AAV vector into a coronary artery or a coronary sinus of an animal in an amount of $1x10^5$ to $1x10^9$ IU/gm, $1x10^7$ IU/gm, or $1x10^6$ to $1x10^8$ IU/gm body weight. Claims 25-30 and 37-39 specify the percentage of cardiomyocytes being tranduced by the AAV virus and number of minutes the AAV virus IU is infused into coronary artery.

The teachings of Hammond is as discussed above under 35 U.S.C. 102(a) rejection. Hammond does not specifically teach the percentage of cardiomyocytes being tranduced by the AAV virus and number of minutes the AAV virus IU is infused into coronary artery.

It would have been obvious for one of ordinary skill in the art at the time of the invention to evaluate the percentage of the cardiomyocytes being transduced and to have 10%, 40%, or 50% of cardiomyocytes being transduced by the AAV virus vector by adjusting the amount of the AAV virus injected. It also would have been obvious for one of ordinary skill in the art at the time of the invention to inject AAV virus into coronary artery for about 2 minutes to 30 minutes, 5 minutes to 20 minutes, or about 15 minutes because the amount of AAV virus administered in the present invention is taught by Hammond and the time required to administer said amount of AAV virus depends on how many virus particles are administered per minute.

One having ordinary skill at the time the invention was made would have been motivated to do so in order to provide sufficient AAV virus to the target cardiomyocytes in a patient so as to obtain therapeutic effect for treating congestive heart failure as taught by Hammond with reasonable expectation of success.

Conclusion

No claim is allowed.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Shin-Lin Chen whose telephone number is (703) 305-1678. The examiner can normally be reached on Monday to Friday from 9:30 am to 6 pm.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Deborah Reynolds can be reached on (703) 305-4051. The fax phone number for this group is (703) 872-9306.

Any inquiry of a general nature or relating to the status of this application should be directed to the Group receptionist, whose telephone number is (703) 308-0196.

Shin-Lin Chen, Ph.D.

Deborah Reynolds

DEBORAH J. REYNOLDS
SUPERVISORY PATENT EXAMINER
TECHNOLOGY CENTER 1600